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Annals of Oncology 26: 838–847, 2015

doi:10.1093/annonc/mdl527

Published online 19 November 2014

Available evidence and new biological perspectives on medical treatment of advanced thymic epithelial tumors

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Received 29 July 2014; revised 16 October 2014; accepted 27 October 2014

Thymic epithelial tumors (TETs) are rare primary mediastinal tumors arising from thymic epithelium. Their rarity and complexity hinder investigations of their causes and therapy development. Here, we summarize the existing knowledge regarding medical treatment of these tumors, and thoroughly review the known genetic aberrations associated with TETs and the present status of potential biological treatments. Epidermal growth factor receptor (EGFR), stem-cell factor receptor, insulin-like growth factor-1 receptor (IGF1R), and vascular endothelial growth factors (VEGF-A, VEGF-B, and VEGF-2) are overexpressed in TETs. EGFR overexpression in TETs is associated with higher stage, and IGF1R overexpression has poor prognostic value. Data indicate that anti-IGF1R monoclonal antibodies, and inhibitors of angiogenesis, somatostatin receptors, histone deacetylase, mammalian target of rapamycin, and cyclin-dependent kinases may be active against TETs. Continued investigations in this field could lead to advancement of targeted and biological therapies for TETs.

Key words: thymic epithelial tumors, thymoma, thymic carcinoma, chemotherapy, biological agents, targeted therapy

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thymic epithelial tumors

Epithelial tumors of thymus are rare cancers and epidemiological data are limited.

In Europe, the incidence rate (period of diagnosis 1995–2002) was 1.4 per 1 000 000 for thymoma (T) [1, 2]. In United States, the overall incidence of T was 1.3 per 1 000 000 person years [3]. The majority of patients with T present with early-stage disease, whereas nearly three-quarters of patients with thymic carcinoma (TC) present with locally advanced or metastatic disease. Five-year survival varied significantly among patients with T compared with TC: more than 80% and ~40%, respectively [4, 5]. In detail, 5-year survival was 88% [95% confidence interval (CI) 59.4–96.9], 83% (95% CI 64–93), 82% (95% CI 61–92), 82% (95% CI 67–91), 54% (95% CI 33–70), 38% (95% CI 20–55) for T (A, AB, B1, B2, B3, and C), respectively [5]. Five-year survival varied also by stage: from 80% to 90% for stage I and II, from 60% to 70% for stage III, from 44% to 55% for stage IV [4–6].

According to the World Health Organization (WHO) histological classification, T includes five entities (types A, AB, B1, B2, and B3) and is the most common primary anterior mediastinal mass, whereas TC is much more rare but much more likely to spread [7]. The causes of thymic epithelial tumors (TETs) remain unknown, but our general knowledge of the involved aberrant pathways is improving. The thymus is the site of T-cell maturation, playing a central role in adaptive immunity, and patients with TETs often also present systemic autoimmune syndromes, including myasthenia gravis autoantibodies to acetylcholine receptors, pure red cell aplasia (PRCA), and hypogammaglobulinemia. The natural history of the disease is usually unpredictable, ranging from asymptomatic incidentally discovered disease with an indolent course to aggressive malignant tumors.

The rarity of this tumor type has precluded it from large phase II and III clinical trial investigations, and new drug development for TET treatment has progressed slowly. Systemic chemotherapy currently represents the standard of care for metastatic or inoperable refractory/recurrent disease, but there remains a lack of standard treatment after first-line failure. In the last decade, several targeted agents have been investigated and the success rates have varied. At present, research on the use of targeted agents in TETs is ongoing. In the present narrative review, we emphasize the most relevant current information regarding the medical treatment of advanced TETs, with a focus on targeted therapies.

chemotherapy

Patients with advanced TETs are candidates for chemotherapy. Adjuvant chemotherapy is not recommended for radically resected (R0) stage I–II TETs. Induction therapy followed by surgery may be useful for thymic malignancies that are initially considered unresectable [8]. Platinum-based combinations remain the standard of care.

Due to the rarity of TETs, published experiences with chemotherapy are limited to anecdotal case reports, retrospective analyses, and small prospective trials, leaving room for debate regarding treatment decisions. Ts are chemotherapy-sensitive, with an average of two thirds of patients showing an objective

response rate (ORR) and one-third showing a complete response (CR), and durable remissions produced in patients with advanced or metastatic Ts. However, the median duration of response varies dramatically among studies, ranging from 1 to more than 7 years. Chemosensitivity has been observed to vary according to the different histological subtypes, with TC considered the least responsive. Table 1 depicts the designs and main outcomes of previous studies of the use of chemotherapy in TETs.

single-agent chemotherapy

There are few documented experiences with the use of single-agent chemotherapy (cisplatin, ifosfamide, and pemetrexed) for patients with advanced T. The Eastern Cooperative Oncology Group (ECOG) evaluated cisplatin (50 mg/m² every 3 weeks) in patients with advanced/metastatic T in a prospective phase II trial. In this study, 21 patients were eligible for assessment, of whom 2 (10%) demonstrated partial remission (PR) and none showed CR. Median overall survival (OS) was 76 weeks, with a 2-year survival rate of 39% [9].

British investigators retrospectively examined the use of ifosfamide as single-agent therapy for T, and reported that the most common toxicities were nausea, vomiting, and leucopenia. Among the 13 assessable patients, the ORR was 46.2%, with five cases showing CR and one PR. Two of the patients had TC and showed stable disease (SD) as the best response to therapy. The median duration of CR was 66 months, and the estimated 5-year survival rate after ifosfamide therapy was 57% [10].

A phase II study evaluated the administration of pemetrexed 500 mg/m² every 3 weeks for a maximum of six cycles among 27 patients with previously treated, unresectable, stage IVA or stage IVB recurrent thymic malignancies [11]. Results were reported only as abstract: of the 23 fully assessable patients, 2 showed CR and 2 PR. Each of these four responding patients had stage IVA disease. Among the total population, median time to progression (TTP) was 45 weeks (45.4 weeks for T versus 5.1 weeks for TC), and OS was 29 months. Toxicity was mild, with no patient experiencing grade IV adverse events. Overall, the preliminary available data indicate that single-agent pemetrexed could be an active agent in a heavily pretreated population of patients with recurrent Ts, but has limited activity in TCs.

polychemotherapy

Cisplatin-based polychemotherapy currently represents the standard of care for TETs. The role of anthracyclines is important; a recent meta-analysis of clinical trials and retrospective investigations compared the efficacy of platinum with anthracyclines versus platinum with nonanthracycline-based chemotherapy in both Ts and TCs, showing a 69.4% response rate [95% confidence interval (CI) 63.1% to 75.0%] for platinum with anthracycline-based chemotherapy and 37.8% (95% CI 28.1% to 48.6%; $P < 0.0001$) for platinum with nonanthracycline-based chemotherapy for Ts whereas the response rates with anthracycline-based and nonanthracycline-based chemotherapy for TCs were similar (40.2% versus 41.2%; $P < 0.89$) [31].

In the early 1990s, the ADOC regimen (doxorubicin, cisplatin, vincristine, and cyclophosphamide) was tested in the

Table 1. Single-agent and combination chemotherapies for TETs

Reference	Study population (N)	Study treatment	Main outcomes	Comment(s)
Single-agent therapy				
Bonomi et al. [9]	21	Cisplatin	ORR 10% (2 PR) OS 76 weeks 2-year surgery 39%	Phase II trial
ECOG				
Highley et al. [10]	15	Ifosfamide	ORR 46.2% (5 CR and 1 PR) 5-year surgery 57%	Retrospective series
Loehrer et al. [11]	27	Pemetrexed	ORR 17% T-group ORR 25% (2 CR and 2 PR) TC-group ORR 9% (1 PR) OS 29 months	Phase II trial Second line
Platinum and anthracycline-based regimens				
Fornasiero et al. [12]	32	Doxorubicin, cisplatin, vincristine, cyclophosphamide (ADOC)	ORR 91% CR 47% TTP 11 months OS 15 months	Retrospective series All patients with T
Rea et al. [13]	16	Doxorubicin, cisplatin, vincristine, cyclophosphamide (ADOC) (+S)	ORR 100% CR 43% 3-year surgery 70% OS 66 months	Retrospective series All patients with T
Koizumi et al. [14]	8	Doxorubicin, cisplatin, vincristine, cyclophosphamide (ADOC)	ORR 75% OS 19 months	Retrospective series All patients with TC 3 patients in second line
Berruti et al. [15]	16	Doxorubicin, cisplatin, vincristine, cyclophosphamide (ADOC) (+S ± RT)	ORR 81% CR 12% TTP 33 months OS 47 months	Phase II All patients with T
Loehrer et al. [16]	30	Doxorubicin, cisplatin, cyclophosphamide (PAC)	ORR 50% CR 10% TTP 18 months OS 38 months	Phase II 29 patients with T
ECOG-SWOG-SEC SG				
Loehrer et al. [17]	23	Doxorubicin, cisplatin, cyclophosphamide (PAC) (+RT)	ORR 70% CR 22% TTP 93 months OS 93 months 5-year surgery 52%	Phase II 21 patients with T
Shin et al. [18]	13	Doxorubicin, cisplatin, cyclophosphamide (PAC + Prednisone (+RT + S)	ORR 92% CR 25% PR 67% 7-year surgery 100% 7-year DFS 73%	Phase II All patients with T
Kim et al. [8]	22	Doxorubicin, cisplatin, cyclophosphamide (PAC + Prednisone (+RT + S)	ORR 77% CR 14% PR 63% 5 year surgery 95% 7-year surgery 77%	Phase II All patients with T
Yokoi et al. [19]	14	Doxorubicin, cisplatin, methylprednisolone (CAMP) (±RT or S)	ORR 92% OS 30 months	Retrospective series
Macchiarini et al. [20]	7	Cisplatin, epirubicin, etoposide (PEpE) (+S + RT)	ORR 100% 2-year surgery 80%	Phase II All patients with T
Lucchi et al. [21]	36	Cisplatin, epirubicin, etoposide (PEpE) (+S ± RT)	OS 113 months 10-year surgery 46% (stage III)–48% (stage IVA)	Retrospective series 12 patients not treated with CT

Continued

Table 1. *Continued*

Reference	Study population (N)	Study treatment	Main outcomes	Comment(s)
Platinum-based regimens				
Giaccone et al. [22] EORTC	16	Cisplatin + etoposide (PE)	ORR 56% PFS 2.2 years OS 4.3 years	Phase II All patients with T
Mineo et al. [23]	33	Cisplatin + etoposide (PE) (+S + RT)	ORR 37% OS 30 months 5-year surgery 37%	Retrospective series All patients with T
Loehrer et al. [24] ECOG	34	Cisplatin + ifosfamide + etoposide (VIP)	ORR 32% OS 32 months	Phase II
Grassin et al. [25]	18	Cisplatin + ifosfamide + etoposide (VIP)	ORR 25% 1-year surgery 94% 2-year surgery 78%	Phase II
Igawa et al. [26]	11	Carboplatin + paclitaxel	ORR 36% PFS 8 months OS 23 months	Retrospective series All patients with TC
Furugen et al. [27]	16	Carboplatin + paclitaxel	ORR 37% CR 12% PR 25% PFS 9 months OS 49 months	Retrospective series All patients with TC
Lemma et al. [28]	46	Carboplatin + paclitaxel	ORR 42.9 (T) ORR 21.7% (TC) PFS 16.7 months (T) PFS 5 months (TC) OS 20 months (TC)	Phase II 23 patients with TC OS not reached for T
Takeda et al. [29] WJOG	40	Carboplatin + paclitaxel	ORR 36% PFS 8 months 1-year surgery 85% 2-year surgery 71%	Phase II All patients with TC
Okuma et al. [30]	9	Cisplatin + irinotecan	ORR 56% PFS 8 months OS 34 months 1-year surgery 78% 2-year surgery 56%	Retrospective series All patients with TC

ORR, overall response rate; OS, overall survival, CR, complete response; TTP, time to progression; PR, partial response; PFS, progression-free survival; RT, radiotherapy; EORTC, European Organization for Research and Treatment of Cancer.

first-line setting, and showed an ORR of 92% and an OS of 15 months [12]. Similar results were shown in successive retrospective series in both T [13] and TC [14]. A phase II trial of 16 patients treated with ADOC regimen confirmed prospectively its activity: ORR was 81% with a DFS of 33.2 months and a median OS of 47.5 months [15].

Another study demonstrated that a three-drug combination of cisplatin, doxorubicin, and cyclophosphamide (PAC or CAP) was associated with an ORR of 50% and an OS of 38 months [16]. The European Organization for Research and Treatment of Cancer investigated cisplatin and etoposide in 16 patients, and reported an ORR of 56% and an OS of 4.3 years [22]. Notably, another study in 28 patients found that the addition of ifosfamide to this doublet (the so-called VIP schedule) resulted in PR in 32% of cases [24]. Carboplatin (area under the curve 6) plus paclitaxel (225 mg/m²) administered every 3 weeks was demonstrated to have modest clinical benefit, showing an ORR

of 42.9% and PFS of 16.7 months among patients with T, and an ORR of 21.7% and PFS of 5.0 months for those with TC [28]. Median OS was not reached among the patients with T, and was 20.0 months in subjects with TC.

second-line chemotherapy

Second-line chemotherapy includes etoposide, ifosfamide, pemetrexed, 5-FU or analogs, gemcitabine, and paclitaxel. A phase II trial investigated the administration of capecitabine (1300 mg/m² on days 1–14) and gemcitabine (1000 mg/m² on days 1 and 8) every 3 weeks in 15 pretreated patients, and the preliminary results demonstrated an ORR of 40% with acceptable toxicity, and 1- and 2-year survival rates of 80% and 67%, respectively [32]. The final analysis of the trial results was recently presented at the ASCO annual meeting [33]: among 30 patients, 3 showed CR and 8 PR, with a PFS of 11 months.

molecular aberrations in TETs and biological treatment approaches

The molecular aberrations underlying thymic malignancies are poorly understood and lack valid preclinical models. The heterogeneity among subtypes and the rarity of the disease make it difficult to investigate relevant genetic alterations. Insights into the biology of thymic tumors have mainly been attained based on anecdotal clinical responses to targeted therapies [34–39]. Some studies have investigated the possibility of exploiting these insights to develop biological and targeted therapies for TETs. These include inhibitors of stem-cell factor receptor (SCFR/KIT/CD117), vascular endothelial growth factor (VEGF) receptor (VEGFR), epidermal growth factor receptor (EGFR), insulin-like growth factor-1 receptor (IGF1R), somatostatin (SST) receptors, histone deacetylase (HDAC), tropomyosin-related kinase A (TrkA), cyclin-dependent kinase (CDK), sarcoma protein (Src), and mammalian target of rapamycin (mTOR).

More recently, data using array-comparative genomic hybridization and next generation sequencing have identified a number of genetic alterations providing a new perspective of the molecular aberrations that differentiate indolent thymomas from more aggressive thymomas and TCs.

In particular, the recurrent GTF2I mutations, which encodes TFII-I, occur with a very high frequency in indolent tumors and represent a marker of favorable prognosis that may be useful in the classification of these rare tumors [40].

The molecular markers BCL2 and CDKN2A may be of potential value in diagnosis and prognosis of TETs and preclinical studies suggested that deregulated antiapoptotic BCL2 family proteins may represent suitable targets for TET treatment [41]. Furthermore, recurrent mutations of KIT were found [40, 42]; however, their clinical role is still to be defined.

Table 2 summarizes the design and the main outcomes of available studies on targeted therapies for advanced TETs.

epidermal growth factor receptor

EGFR is one of the most studied biomarkers in epithelial cancers. Several studies have used immunohistochemistry (IHC) to investigate EGFR expression levels in thymic tumors [62–69]. EGFR is reportedly overexpressed in 70% of Ts and 53% of TCs, with higher EGFR staining significantly associated with stage III–IV tumors. EGFR copy number seems significantly amplified in type B3 Ts. The degree of this EGFR amplification, as measured by fluorescence *in situ* hybridization, poorly correlates with EGFR overexpression but is significantly associated with stage II–IV tumors [70]. EGFR mutations are rare in thymic malignancies [39, 43, 62, 66, 68]. Among 158 analyzed tumors, only 3 EGFR mutants were found, all of which were missense mutations in exon 21 (2 cases of L858R and 1 case of G863D). No mutations were detected in exons 18 and 19. There is no reported correlation between EGFR expression and EGFR mutational status.

A phase II trial, available only as an abstract, examined the results of gefitinib administration (250 mg orally daily) among 26 pretreated patients with stage IV TETs achieving only one partial response. [43]. It is likely that thymic tumors rarely respond to EGFR inhibitors due to the low frequency of EGFR-

activating mutations in these tumors. Another abstract described a phase II trial included 18 chemorefractory patients with limited clinical benefit, and assessed the effects of administering a combination of erlotinib (150 mg PO daily) and bevacizumab (15 mg/kg i.v. every 3 weeks) without any interesting results. [44]. Only two case reports described activity of cetuximab in heavily pretreated recurrent Ts [38, 71]. An ongoing phase II trial is evaluating cetuximab in combination with a CAP regimen for treatment of unresectable thymomas (clinicaltrials.gov NCT01025089). Although single-case observations suggest that EGFR targeting may be effective in some patients, two clinical phase II studies using erlotinib and gefitinib in a total of 44 patients resulted in no complete remission and only two partial responses. Based on available evidence, the role of inhibiting EGFR in T and TC seems promising but it is still to be clarified.

stem-cell factor receptor

KIT is a transmembrane growth factor with tyrosine kinase activity, and its ligand is the stem-cell factor (SCF). KIT is overexpressed in 2% of Ts and 79% of TCs [72]. Although 80% of TCs reportedly overexpress KIT protein, only 9% show KIT mutations [73], with a V560 deletion detected in two cases, one missense mutation in exon 11 (L576P substitution), a D820E mutation found in a patient responding to sorafenib, and an H697Y mutation in exon 14 in a case with high sensitivity to sunitinib *in vitro*. Among the known mutations, V560 deletions and the L576P substitution are sensitive to imatinib [34].

Phase II trials evaluated the effects of imatinib in B3 Ts and TCs—which were selected based on KIT staining by IHC rather than genotyping—and reported negative results [47]. A small phase II trial evaluated imatinib (600 mg PO daily) in seven patients with TETs, and found that two patients had SD and five progressed, the median OS was 4 months, and median TTP was 2 months. Samples from four patients were analyzed by IHC, which revealed KIT expression in one sample. Three samples were analyzed for mutations in the KIT or PDGFRA genes, revealing no mutations. The authors concluded that imatinib has no major activity in this tumor; however, these results may have been influenced by the small number of patients and lack of selection criteria [45]. A second trial investigated imatinib administration in 11 patients with pretreated, advanced, unresectable TCs. KIT expression was confirmed by IHC staining in nine patients, and PDGFR in two patients. No objective response was reported in the abstract [46]. Finally, a third phase II trial of imatinib (400 mg PO daily) in 15 pretreated patients reported no response, with a median PFS of 3 months. None of the patients harbored a known KIT activating mutation. Three of the included patients had TCs, of whom two presented KIT expression on IHC [47].

insulin-like growth factor-1 receptor

IGF1R is a transmembrane receptor that is frequently overexpressed in squamous cell carcinomas, and that apparently plays roles in multiple processes related to oncogenesis. IGF1R can form heterodimers with EGFR, which promotes resistance to EGFR inhibitors. In a cohort of 63 thymic tumors, IGF1R

Table 2. Targeted therapies in TETs

Reference	Study population (N)	Study treatment	Main outcomes	Comment(s)
EGFR inhibitors				
Kurup et al. [43]	26	Gefitinib	ORR 1% 14 SD TTP 4 months	Phase II
Bedano et al. [44]	18	Erlotinib + Bevacizumab	ORR 0% 11 SD	Phase II
KIT inhibitors				
Giaccone et al. [45]	9	Imatinib	ORR 0% 2 SD OS 4 months TTP 2 months	Phase II 7 patients with TC
Salter et al. [46]	11	Imatinib	ORR 0%	Phase II All patients with TC
Palmieri et al. [47]	15	Imatinib	ORR 0% 1 SD PFS 3 months	Phase II 3 patients with TC
IGF1R inhibitors				
Haluska et al. [48]	1	Figitumumab	SD	Phase I
Rajan et al. [49]	49	Cixutumumab	ORR 10% 33 SD	Phase II All patients with TC
Angiogenesis inhibitors				
Bedano et al. [44]	18	Erlotinib + Bevacizumab	ORR 0% 11 SD	Phase II
Isambert et al. [50]	1	Aflibercept + Docetaxel	PR	Phase I
Thomas et al. [51]	23 TCs/16 Ts	Sunitinib	• TC • ORR 26% • OS 16.3 months	Phase II
NCT01621568			• T • ORR 6% • 12 SD • PFS 8.5 months • OS	
Fiedler et al. [52]	4	SU014813	2 PR (PFS 15.3 and 9.0 months)	Phase I
Azad et al. [53]	1	Motesanib	SD	Phase I
SSTR inhibitors				
Palmieri et al. [54]	16	Octreotide + Prednisone	ORR 37% OS 15 months	Phase II
Loehrer et al. [55]	38	Octreotide ± Prednisone	ORR 30%	Phase II
Longo et al. [56]	12	Long-acting octreotide	3 PR (25%) 5 SD (42%) PFS 8 months	Retrospective experience
HDAC inhibitors				
Steele et al. [57]	1	Belinostat	SD	Phase I
Giaccone et al. [58]	41	Belinostat	2 PR 25 SD	Phase II 16 patients with TC
CDK inhibitors				
Besse et al. [59]	30	Milciclib maleate	1 PR 13 SD PFS-3 rate 46.7% Ongoing	Phase II
NCT01011439				
Src inhibitors				
Wakelee et al. [60]	21	Saracatinib	No efficacy	Phase II 7 patients with TC
mTOR inhibitors				
Zucali et al. [61]	35	Everolimus	1 CR 3 PR 21 SD Ongoing	Phase II
NCT02049047				

ORR, overall response rate; SD, stable disease; TTP, time to progression; OS, overall survival; PFS, progression-free survival; PR, partial response; CR, complete response.

overexpression was found to be more frequent in TCs (86%) than in Ts (43%), and was significantly associated with EGFR overexpression [74]. Girard et al. did not find IGF1R overexpression to be related to TTP. However, Zucali et al. investigated TETs and reported that among IGF1R overexpression carries a poor prognostic value for OS, as well as for TTP among primary tumors [75].

A phase I dose-escalation study in patients with refractory solid tumors reported that the anti-IGF1R monoclonal antibody figitumumab showed clinical activity lasting more than 1 year in a case of refractory T [48]. A very recent multicenter, open-label, phase II trial tested the administration of cixutumumab (IMC-A12, 20 mg/kg i.v. every 3 weeks until disease progression or unacceptable toxicity) in 49 pretreated patients with TETs (37 Ts and 12 TCs) [49]. Among patients with Ts, 5 showed PR and 28 SD, whereas in the TC cohort, only 5 patients experienced SD. However, a relevant number of toxicities were observed such as: hyperglycemia (10%), lipase elevation (6%), and weight loss, tumor pain, and hyperuricemia (4% each). Notably, nine T patients (24%) developed autoimmune conditions during treatment, including five new-onset disorders, the most common of which was PRCA.

vascular endothelial growth factors and VEGF receptors and angiogenesis inhibitors

VEGF and VEGFR are the most potent proangiogenic molecules, and VEGF-A, VEGFR-1, and VEGFR-2 are overexpressed in both Ts and TCs [76]. Microvessel density and VEGF expression levels have been shown to correlate with tumor invasion and clinical stage in TETs [77]. Increased serum levels of VEGF are observed in patients with TCs but not in those with Ts [78].

While it is known that TETs overexpress VEGF and VEGFRs, limited data exist regarding the efficacy of angiogenesis inhibitors in these tumors. Isambert et al. conducted a phase I trial [50] and reported that a patient with T experienced a PR following administration of the combination of aflibercept (a soluble receptor that binds VEGF-A; also called VEGF trap) and docetaxel. Multikinase inhibitors may also be of interest for targeting angiogenesis. A patient who presented a missense mutation in exon 17 (D820E) of KIT reportedly showed PR following sorafenib treatment [79]. Another patient showed prolonged disease stability of about 9 months in a tumor that lacked mutations but that was demonstrated by IHC to highly express KIT, p53, and VEGF [35]. The activity of sorafenib in TETs was additionally confirmed in a third case report [80] that described a 50% reduction of tumor size lasting for 18 months in patient with a KIT-negative TC. A phase II trial investigated sunitinib administration after failure of platinum-based chemotherapy, and the preliminary data were presented at the 2014 ASCO meeting [51]. Among 23 evaluable TCs, 6 (26%) showed PR and 15 (65%) SD, with 6.7 of PFS and 16.3 months of OS at 13.9 months of follow-up. In contrast, of the 16 Ts, only 1 (6%) showed PR and 12 (75%) had SD, with a PFS of 8.5 months and an OS of 16.3 months after 12.7 months of follow-up. KIT mutations were absent in 20 tumors assessed, which included 11 TCs and 4 cases that showed PR. In conclusion, beyond the

inhibition of KIT, 'sunitinib' and 'sorafenib' also inhibit VEGFR-1, VEGFR-2, and VEGFR-3 at the nanomolar range: the effect of these drugs, especially in KIT-wild-type thymic tumors may then be partially related to an antiangiogenic effect.

In phase I trial of SU14813—a multitargeted tyrosine kinase inhibitor (VEGFRs, PDGFRs, KIT, and FLT-3)—four patients with Ts were treated, and two experienced PR with PFS of 15.3 and 9.0 months [52]. Similar to sunitinib and sorafenib, the VEGFR-1/2/3 inhibitor motesanib diphosphonate (AMG-706) reportedly controlled the growth of an advanced T refractory to chemotherapy for 12 months [53]. A phase II trial tested bevacizumab in combination with erlotinib, and found no tumor response in 11 Ts and 7 TCs [44]. Interestingly, despite the large tumor burden of thymic tumors and the frequent abutment to mediastinal vascular structures, no hemorrhagic side-effects have been reported with the use of these drugs.

somatostatin receptor inhibitors

Octreotide, an octapeptide SST analog with high affinity for SST2 subtype receptor, has been demonstrated to have an inhibitory effect in thymic epithelial cells *in vitro* [81]. A phase II trial enrolled 16 patients treated with s.c. octreotide (1.5 mg daily) plus prednisone (0.6 mg/mq/day orally for 3 months, 0.2 mg/kg/day orally during follow-up). The ORR was 37% and the OS was 15 months [54]. A similar trial was conducted by ECOG in patients with advanced, unresectable, octreotide-scan-positive TETs [55] in which octreotide effect was evaluated alone for two cycles and then, if no objective response was observed, in association with prednisone. Thirty-eight patients (32 Ts, 5 TCs, and 1 thymic carcinoid) received octreotide 0.5 mg s.c. three times daily for up to 1 year. Among these 38 patients during treatment with octreotide alone, 4 (10.5%) showed PR. Among the 21 patients who received prednisone in addition to octreotide, 2 CRs and 6 PRs were noted. The overall ORR was 30.3%, and the 1- and 2-year survival rates were 86.6% and 75.7%, respectively. Eight patients experienced grade 4 or 5 toxicity, including one death that occurred secondary to grade 5 infection without neutropenia. In a more recent retrospective experience, 12 TET patients were treated with long-acting octreotide (20 mg i.m. every 2 weeks) [56]. In total, 3 PR (25%) and 5 SD (42%) were reported, with a mean PFS of 8 months (range, 3–21 months). Treatment compliance and tolerability were judged to be good. An ongoing phase II trial is currently evaluating the effect of pasireotide (SOM230 LAR) in a dosage of 60 mg i.m. administered every 4 weeks among adult patients with inoperable or metastatic T (clinicaltrials.gov NCT02021942).

histone deacetylase inhibitors

In a phase I study of the pan-HDAC inhibitor belinostat (PXD101), a patient with T showed a tumor reduction that lasted for 17 months of treatment [57]. A phase II trial studied the administration of belinostat (1 g/m² on days 1 through 5, every 3 weeks) to 41 patients (25 Ts and 16 TCs), and reported PR in 2T patients, along with 25 SD and 13 PD. TTP was 174 days and OS was 575 days. Treatment was well tolerated, with nausea, vomiting, and fatigue shown to be the major adverse effects [58]. An ongoing phase I/II trial is investigating belinostat in

combination with CAP as first-line therapy for advanced or recurrent thymic malignancies (clinicaltrials.gov NCT 01100944).

tropomyosin-related kinase A and cyclin-dependent kinases inhibitors

Kim et al. [82] used IHC staining to evaluate Trk expression in 99 patients with TET, and found cytoplasmic TrkA immunoreactivity in all tumors except one TC, whereas no tumors showed TrkB or TrkC immunoreactivity. Their results also showed that expression of the neurotrophin receptor p75(NTR) in Ts was correlated with staging.

CDK proteins controlling cell cycle G1-S phase transition may be altered through p16INK4 loss in Ts [83]. Through inhibition of CDK4 and CDK6, P16INK4 prevents RB phosphorylation, leading to G1-S block. The copy number losses of CDKN2A and 13q were identified as potentially poor prognostic markers in TETs, implying that RB pathway deregulation may be important in TET pathogenesis [41]. In the same study, IHC on 132 TETs demonstrated that copy number loss of CDKN2A correlated with lack of expression of its related protein p16(INK4) and identified tumors with poor prognosis. Downregulation of p16 through promoter methylation has been observed in 3%–13% of TETs [83, 84]. No P16INK4 mutations have been described in TETs, whereas gene deletion appears to be related to invasive phenotypes in rat models [85]. Furthermore, decreased expression of the cell cycle proteins p21 and p27 (both CDK inhibitors) is predictive of a poor response to chemotherapy in T [86].

Oral milciclib maleate (PHA-848125-AC)—an oral, potent inhibitor of the CDK2/cyclin Two ongoing phase II studies (clinicaltrials.gov NCT01011439 and NCT01301391) are currently investigating the use of this molecule in pretreated patients with advanced TETs. At the 2014 ASCO annual meeting, preliminary data were presented regarding patients who received one prior line of systemic therapy: of 30 patients for whom mature data were available, 14 cases were successful with a PFS-3 rate of 46.7% (95% CI 28.3% to 65.7%) including PR and with a moderate toxicity profile [59].

Src inhibitors

The SRC family of tyrosine kinases and downstream targets play a crucial role in thymocyte development. A phase II trial investigated saracatinib (AZD0530), a small-molecule inhibitor of Src, in patients with previously treated advanced thymic malignancies. A total of 21 patients (14 Ts and 7 TCs) received 175 mg of saracatinib daily, but the trial was terminated due to a lack of clinical activity [60].

phosphoinositide-3-kinase pathway

No alterations have been reported in the phosphoinositide-3-kinase (PI3K)-catalytic subunit (PIK3CA), phosphatase, and tensin homolog deleted on chromosome 10 (PTEN), protein kinase B (PKB or AKT1), or mTOR. A phase II study is investigating use of the mTOR inhibitor everolimus in TETs previously treated with cisplatin-based chemotherapy. At the 50th ASCO annual meeting, preliminary data were presented from the first enrolled 35 patients in this trial, of whom 25 achieved disease

control as the primary end point: CR in 1 TC, PR in 3 patients (2 TCs/1T), and SD in 21 patients (16 TCs/5 Ts) [61]. The study is still ongoing (clinicaltrials.gov NCT02049047).

expert commentary and 5-year view

The rarity and complexity of TETs has hindered investigations of their causes and slowed the development of advanced and targeted biological treatments. Despite the lack of valid preclinical models and other challenges faced by these studies, our general knowledge of the aberrant pathways involved in TETs development is improving, primarily through insights attained based on anecdotal clinical responses to targeted therapies. To date, data indicates that EGFR, KIT, IGF1R, and several VEGF molecules are overexpressed in TETs. Furthermore, EGFR overexpression in TETs is associated with higher disease stage, and IGF1R overexpression carries poor prognostic value. Clinical data suggest that anti-IGF1R monoclonal antibodies, and inhibitors of angiogenesis, SST receptors, HDAC, mTOR, and CDK may be potentially useful as targeted biological therapies against TETs. While many investigations of biological agents have demonstrated a lack of activity against TETs, the few promising results—for example, in the studies of antiangiogenesis, mTOR, and CDK/TrkA inhibitors—are encouraging and support the continuation of efforts. In upcoming years, we expect that the completion of ongoing trials and initiation of new studies will further advance our knowledge of the causes of and genetic aberrations involved in various types of TETs, leading to development and use of biological therapies that will be particularly useful for managing unresectable cases.

disclosure

The authors have declared no conflicts of interest.

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